

### **REMARKS**

Claims 3-8, 12, 16, and 20-28 are pending in the subject application. Claims 3-7 were previously withdrawn from consideration. Applicant currently amends claims 8, 12, and 16. The claim amendments do not add new subject matter to the application, and are supported by the description at pages 2, 3 and 8. Applicant respectfully requests that Examiner enters the claim amendments.

Examiner rejected claims 8, 12, 16, and 20-28 under 35 U.S.C. 103(a) as obvious over Armour Pharmaceutical Company (EP 0115627) ("APC"), Azria et al., U.S. Patent 5,759,565 ("Azria") and Grebow, et al., U.S. Patent 5,026,825 ("Grebow"). Applicant respectfully traverses the rejection.

Examiner correctly states that Azria does not teach the use of a calcitonin formulation comprising chlorobutanol at a concentration range lower than 0.6% (w/w or w/v) (see the sentence in the Office Action bridging pages 3 and 4). Accordingly, Azria does not disclose or suggest Applicant's claimed invention, which requires, *inter alia*, a calcitonin formulation consisting of calcitonin, between about 0.25% to about 4.0% chlorobutanol; a pH about 3-4, and less than about 5% oxygen.

Examiner relied on APC and Grebow for curing what is missing from Azria, a teaching showing use of chlorobutanol at a concentration range lower than 0.6%. Examiner alleged that APC taught the use of chlorobutanol in the range of 0.001-2% (w/w), and that Grebow taught chlorobutanol in ranges from 0.5-1.0 and at 0.1%. Actually, the disclosure of APC and Grebow are nearly identical with each other with respect to the range of chlorobutanol concentration.

- APC page 7 has the identical range of concentrations as Grebow column 12. Accordingly, APC and Grebow both taught using calcitonin formulations having 0.5 to 1.0% chlorobutanol (w/w).
- Preservative concentrations in Grebow Examples 1-10 are very similar to APC Example 1-10. Both Grebow and APC describe a formulation having 0.1% chlorobutanol in their respective Example 9.

Neither APC nor Grebow taught or suggested Applicant's claimed invention, which requires a calcitonin formulation consisting of calcitonin, between about 0.25% to about

4.0% chlorobutanol; a pH about 3-4, and less than about 5% oxygen. Accordingly, Azria alone or in combination with either or both APC and Grebow fails to teach Applicant's claimed invention.

Examiner alleged that Azria taught calcitonin in a saline solution at a pH of 3-5, and chlorobutanol. Examiner failed to point out that Azria taught a calcitonin formulation requiring a surfactant and/or benzalkonium chloride (see Abstract, col. 2 ll. 52-67, col. 3 l. 56 to col. 4 l. 10, col. 4 l. 31 to col. 5, l. 42, col. 6 l. 45-51, and elsewhere through the description and claims). Applicant's claimed invention is a composition consisting of calcitonin, between about 0.25% to about 4.0% chlorobutanol; a pH about 3-4, and less than about 5% oxygen. Applicant's claimed invention does not include benzalkonium chloride or a surfactant. Accordingly, Azria does not disclose Applicant's invention, which lacks both of those excipients.

The shortcoming of Azria is not remedied by the teaching of either APC or Grebow. APC taught formulations that all required an absorption promoter that include surfactants (surface active agents). See p. 5, l. 5 to p. 6, l. 3, Examples 1-10, p. 1, l. 5-14, Tables I, II and III, and claims. Grebow taught formulations that all required  $\Delta$ -aminolevulinic acid. See Abstract, col. 1 ll. 5-12 and 61-65; col. 2 ll. 24-29; col. 11, ll. 1-12; Examples 1-14, col. 14 ll. 16-39, and the claims. Applicant's claimed invention is a composition consisting of calcitonin, between about 0.25% to about 4.0% chlorobutanol; a pH about 3-4, and less than about 5% oxygen. Applicant's claimed invention does not include  $\Delta$ -aminolevulinic acid or a surfactant. Accordingly, neither APC nor Grebow alone nor either or both reference in combination with Azria taught or suggested Applicant's invention, which lacks benzalkonium chloride,  $\Delta$ -aminolevulinic acid, benzalkonium chloride and/or a surfactant.

Applicant previously argued against combining references, pointed to Azria as teaching away from the claimed invention, by identifying the deleterious effect of using chlorobutanol, and arguing that this effect would chill the motivation of the ordinary worker to turn to another reference also requiring chlorobutanol. Examiner acknowledged the deleterious effect of chlorobutanol as taught by Azria. In response to Applicant's "teaching away" argument, Examiner alleged that knowing the deleterious effects of chlorobutanol at a concentration range at 0.6% or higher would motivate the skilled worker to rely on APC and Grebow, by providing a need to "optimize the concentration parameters to eliminate

undesirable effect of any given component.” Examiner’s argument is incorrect and does not comport to well established case law.

As noted above, Azria taught use of calcitonin solutions comprising either benzalkonium chloride or a surfactant. One of ordinary skill cannot be motivated to “trade-off” the advantages of one reference to combine with another (see *Winner Int’l Royalty Corp. v. Wang*, 53 USPQ2d 1580, 1587 (Fed. Cir. 2000)). Here, Examiner improperly argued that one of ordinary skill would ignore the advantages taught and claimed by Azria, which required solutions with either benzalkonium chloride or a surfactant, while combining the teachings of Azria with those of APC and Grebow to arrive at Applicant’s claimed invention, which required neither benzalkonium chloride nor a surfactant. Moreover, both APC and Grebow required a surfactant or  $\Delta$ -aminolevulinic acid, respectively. Apparently, the advantages taught by Azria were appreciated and adopted by APC and Grebow. An ordinary skilled worker would not “trade-off” underscored advantages that were described and claimed by Azria when combining with APC or Grebow or both. Accordingly, Examiner’s alleged motivation to combine requires trading off the advantages taught in Azria and incorporated into APC and Grebow. For these reasons is a motivation to combine Azria with APC and Grebow is lacking.

For these reasons, Applicant’s claimed invention is patentable over these references individually or in combination. Applicant respectfully requests that Examiner withdraws the instant obviousness rejection of claims 8, 12, 16, and 20-28.

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Applicant respectfully submits that the present case is in condition for allowance. A notice to that effect is respectfully requested.

If at any time, if Examiner considers that a phone discussion would be helpful, the undersigned would appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at 206-332-1390.

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